(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 369 112 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
10.12.2003 Bulletin 2003/50

(51) Int Cl.[7]: **A61K 9/70**, A61K 47/32

(21) Application number: **03012812.8**

(22) Date of filing: **05.06.2003**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

(30) Priority: **05.06.2002 JP 2002164973**

(71) Applicant: **NITTO DENKO CORPORATION**
Osaka (JP)

(72) Inventors:
- **Muraoka, Takateru**
  Ibaraki-shi, Osaka (JP)
- **Inosaka, Keigo**
  Ibaraki-shi, Osaka (JP)
- **Ishitani, Hiroko**
  Ibaraki-shi, Osaka (JP)
- **Nakano, Yoshihisa**
  Ibaraki-shi, Osaka (JP)

(74) Representative: **Grünecker, Kinkeldey,**
Stockmair & Schwanhäusser Anwaltssozietät
Maximilianstrasse 58
80538 München (DE)

(54) Percutaneous absorption-type pharmaceutical preparation and process for producing the same

(57) The present invention provides a stable percutaneous absorption-type pharmaceutical preparation for the percutaneous absorption of basic drugs which does not cause a decrease in the cohesive force of the pressure-sensitive adhesive layer even in the presence of sweat components due to perspiration during wear; and a process for producing the pharmaceutical preparation. The percutaneous absorption-type pharmaceutical preparation comprises a substrate and, superposed on one side thereof in this order, a pressure-sensitive adhesive layer (A) comprising a pressure-sensitive adhesive and a basic drug and a pressure-sensitive adhesive layer (B) comprising a pressure-sensitive adhesive crosslinked with a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate compound.

EP 1 369 112 A1

Printed by Jouve, 75001 PARIS (FR)

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a percutaneous absorption-type pharmaceutical preparation for percutaneously administering a basic drug and a process for producing the same.

BACKGROUND OF THE INVENTION

[0002] Various patch type pharmaceutical preparations including poultices and tape preparations are recently being developed as percutaneous absorption-type pharmaceutical preparations for administering a drug to the living body through the skin. Of these preparations, tape preparations containing a drug which exerts a systemic pharmacological action are especially attracting attention. For example, percutaneous absorption-type pharmaceutical preparations in a tape form which contain any of nitroglycerin, isosorbide dinitrate, various steroidal drugs, non-steroidal drugs, anesthetics, antihypertensive agents, and the like as an active ingredient in the pressure-sensitive adhesive layer were proposed, and some of them have come into the market. These percutaneous absorption-type pharmaceutical preparations employ an acrylic or synthetic-rubber-based pressure-sensitive adhesive containing any of various percutaneously absorbable drugs. Upon mere application to the skin, the drug is constantly absorbed into the body through the skin to show an excellent pharmacological action.

[0003] Percutaneous absorption-type pharmaceutical preparations for the continuous percutaneous administration of drugs for treatments for or prevention of various diseases are desired to have sufficient adhesion to the skin and give an excellent wear feeling. In addition, the preparations are desired to have such a property that stripping thereof from the skin after wear does not result in the trouble in which the adhesive partly remains on the skin surface, i.e., the so-called adhesive remaining. However, percutaneous absorption-type pharmaceutical preparations heretofore in use, in particular, percutaneous absorption-type pharmaceutical preparations for the percutaneous absorption of basic drugs, have had a problem that properties of the pressure-sensitive adhesive change during wear and the pressure-sensitive adhesive layer tends to show a cohesive failure upon stripping, resulting in adhesive remaining.

[0004] On the other hand, a percutaneous absorption-type pharmaceutical preparation, after application to the skin, blocks up sweat glands in the skin and, as a result, perspiration occurs to cause, e.g., a phenomenon in which sweat resides between the skin and the percutaneous absorption-type pharmaceutical preparation. The degree of this perspiration varies considerably depending on the seasons. The sweat of the human being is mostly accounted for by water, and excessive perspiration causes the percutaneous absorption-type pharmaceutical preparation to peel off the skin or exerts other influences. The sweat contains various components besides water, such as lactic acid, urea, ammonia, and inorganic salts.

[0005] However, it has hitherto been thought that the influences of perspiration are within the range of fluctuations attributable to differences among individuals, seasonal differences, etc., and investigations for diminishing the influences of perspiration have been directed only toward minor modifications such as property improvements in pressure-sensitive adhesives and addition of additives or other ingredients. No sufficient investigation has been made on the stability of a percutaneous absorption-type pharmaceutical preparation in relation to sweat components, especially sweat components other than water.

SUMMARY OF THE INVENTION

[0006] An object of the invention is to provide a stable percutaneous absorption-type pharmaceutical preparation for the percutaneous absorption of basic drugs which does not suffer a decrease in the cohesive force of the pressure-sensitive adhesive layer even in the presence of sweat components due to perspiration during wear and which is free from a cohesive failure and resultant adhesive remaining when stripped off. Another object of the invention is to provide a process for producing the pharmaceutical preparation.

[0007] The present inventors made intensive investigations in order to accomplish those objects. As a result, they have found that in percutaneous absorption-type pharmaceutical preparations containing a basic drug, the lactic acid contained in sweat is taken up by the pressure-sensitive adhesive layer under the influence of the basic drug and this lactic acid acts on crosslinks in the pressure-sensitive adhesive, which have been formed with a specific crosslinking agent, i.e., an organometallic compound, metal alcoholate, or metal chelate compound, to reduce the cohesive force of the pressure-sensitive adhesive layer. When this pharmaceutical preparation is stripped off, the reduced cohesive force of the pressure-sensitive adhesive layer results in a tendency to cohesive failure and hence causes the phenomenon of adhesive remaining. On the other hand, it has been found that when a crosslinking agent which forms crosslinks unsusceptible to the influence of lactic acid (e.g., a polyisocyanate compound) is used for crosslinking a pressure-sensitive adhesive containing a basic drug, then the formation of crosslinks is inhibited by the basic drug contained in

the adhesive.

[0008] The inventors have further found that when a pressure-sensitive adhesive layer comprising a basic drug and either a pressure-sensitive adhesive crosslinked with a crosslinking agent which is not inhibited from forming crosslinks by the presence of the basic drug, e.g., a crosslinking agent such as an organometallic compound, metal alcoholate, or metal chelate compound, or an uncrosslinked pressure-sensitive adhesive is formed on one side of a substrate and a pressure-sensitive adhesive layer comprising a pressure-sensitive adhesive crosslinked with a crosslinking agent which forms crosslinks unsusceptible to the influence of lactic acid, i.e., a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate compound, is formed on that pressure-sensitive adhesive layer, i.e., on the side to be applied to the skin, then a stable pharmaceutical preparation can be obtained which does not cause a decrease in the cohesive force of the pressure-sensitive adhesive layers even when the lactic acid in sweat is taken up and which is free from adhesive remaining when stripped off. Thus, the present invention has been completed.

[0009] The invention provides the following.

[1] A percutaneous absorption-type pharmaceutical preparation which comprises a substrate and, superposed on one side thereof in this order, a pressure-sensitive adhesive layer (A) comprising a pressure-sensitive adhesive and a basic drug, and a pressure-sensitive adhesive layer (B) comprising a pressure-sensitive adhesive crosslinked with a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate compound.

[2] The percutaneous absorption-type pharmaceutical preparation described in [1] above wherein the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) is a pressure-sensitive adhesive crosslinked with one or more crosslinking agents selected from the group consisting of polyisocyanate compounds, organic peroxides, melamine derivatives, polyfunctional compounds, amino resins, silane compounds, diol compounds, polyol compounds, bisphenol compounds, and sulfides.

[3] The percutaneous absorption-type pharmaceutical preparation described in [1] or [2] above wherein at least one of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive layer (B) contain a liquid plasticizing ingredient.

[4] The percutaneous absorption-type pharmaceutical preparation described in any one of [1] to [3] above wherein the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) have the same composition.

[5] The percutaneous absorption-type pharmaceutical preparation described in any one of [1] to [4] above wherein at least one of the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) each are an acrylic copolymer pressure-sensitive adhesive.

[6] The percutaneous absorption-type pharmaceutical preparation described in [5] above wherein the acrylic copolymer pressure-sensitive adhesive of each of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive layer (B) comprises a copolymer obtained by copolymerizing from 60 to 98% by weight of at least one alkyl (meth)acrylate in which the alkyl has 4 to 12 carbon atoms with from 2 to 40% by weight of at least one functional monomer.

[7] The percutaneous absorption-type pharmaceutical preparation described in [6] above wherein the functional monomer is a monomer having one or more substituents selected from the group consisting of a carboxyl group, a hydroxyl group, a sulfo group, an amino group, an amido group, an alkoxyl group, a cyano group, and an acyloxy group.

[8] The percutaneous absorption-type pharmaceutical preparation described in [7] above wherein the functional monomer is one or more monomers selected from the group consisting of (meth)acrylic acid, 2-hydroxyethyl (meth) acrylate, styrenesulfonic acid, (meth)acrylamide, vinylpyrrolidone, 2-aminoethyl (meth)acrylate, acrylonitrile, 2-methoxyethyl (meth)acrylate, and vinyl acetate.

[9] A process for producing a pharmaceutical preparation of the percutaneous absorption-type which comprises:

(1) a step of forming a pressure-sensitive adhesive layer (A) comprising a pressure-sensitive adhesive and a basic drug on one side of a substrate; and

(2) a step of crosslinking a pressure-sensitive adhesive with a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate compound in the absence of any basic drug to obtain a crosslinked pressure-sensitive adhesive and forming a pressure-sensitive adhesive layer (B) comprising the crosslinked pressure-sensitive adhesive on the pressure-sensitive adhesive layer (A).

DETAILED DESCRIPTION OF THE INVENTION

[0010] The invention will be explained below in detail.

[0011] The substrate to be used in the percutaneous absorption-type pharmaceutical preparation of the invention is not particularly limited. However, it is preferably made of a material which prevents the drug and other additives (e.g., a plasticizer and an absorption accelerator), incorporated in the pressure-sensitive adhesive layers from passing through the substrate and going out from the back side to result in a decrease in content. Namely, the substrate is preferably made of a material impermeable to these ingredients.

[0012] Examples of the substrate include films of single materials, such as films of polyesters (e.g., poly(ethylene terephthalate)), polyamides (e.g., nylons), polyolefins (e.g., polyethylene and polypropylene), poly(vinyl chloride), plasticized poly(vinyl chloride), plasticized vinyl acetate/vinyl chloride copolymers, poly(vinylidene chloride), ethylene/vinyl acetate copolymers, cellulose acetate, ethyl cellulose, ethylene/ethyl acrylate copolymers, polytetrafluoroethylene, polyurethanes, and ionomer resins and metal foils, e.g., aluminum foils. Examples thereof further include laminated films comprising a combination of two or more of these films.

[0013] The thickness of the substrate is not particularly limited. However, from the standpoint of not impairing soft feeling of the percutaneous absorption-type pharmaceutical preparation, the substrate thickness is generally from 1 to 25 μm, preferably from 1 to 15 μm.

[0014] The substrate preferably has a porous film laminated thereto so as to improve the anchoring (adhesion) of the pressure-sensitive adhesive layer to the substrate. In this case, the pressure-sensitive adhesive layers are formed on the porous-film side.

[0015] Examples of this porous film include papers, woven fabrics, nonwoven fabrics, and mechanically perforated films.

[0016] The pressure-sensitive adhesive to be used in the pressure-sensitive adhesive layer (A) is not particularly limited as long as it has pressure-sensitive adhesive properties at ordinary temperature. However, acrylic copolymer pressure-sensitive adhesives are preferred from the standpoints of adhesion to the skin, drug solubility, drug stability, etc. A single pressure-sensitive adhesive or a combination of two or more pressure-sensitive adhesives may be used. The acrylic copolymer pressure-sensitive adhesives are not particularly limited, and examples thereof include copolymers of at least one alkyl (meth)acrylate with at least one functional monomer. The term "functional monomer" as used herein means a monomer having at least one unsaturated double bond in the molecule and further having a functional group as or in a side chain. The copolymers of at least one alkyl (meth)acrylate with at least one functional monomer preferably are copolymers obtained by copolymerizing from 60 to 98% by weight, preferably from 65 to 97% by weight, of at least one alkyl (meth)acrylate with from 2 to 40% by weight, preferably from 3 to 35% by weight, of at least one functional monomer (provided that the sum of the monomers is 100% by weight).

[0017] Examples of the alkyl (meth)acrylate include the esters obtained from acrylic or methacrylic acid and linear or branched, primary, secondary, or tertiary alcohols in which the alkyl group has 4 to 12 carbon atoms.

[0018] Specific examples of the alkyl (meth)acrylate include butyl (meth)acrylate, pentyl (meth)acrylate, hexyl (meth) acrylate, heptyl (meth)acrylate, octyl (meth)acrylate, nonyl (meth)acrylate, decyl (meth)acrylate, undecyl (meth)acrylate, dodecyl (meth)acrylate, and 2-ethylhexyl (meth)acrylate.

[0019] Examples of the functional monomer include functional monomers having at least one unsaturated double bond in the molecule and further having one or more functional groups selected, for example, from the group consisting of carboxyl, hydroxyl, sulfo, amino, amido, alkoxyl, cyano, and acyloxy groups as or in a side chain. Specific examples of the functional monomer include alkoxyl-modified alkyl (meth)acrylate monomers obtained by modifying the alkyl group of an alkyl (meth)acrylate with a linear or branched alkoxyl group having 1 to 4 carbon atoms (e.g., methoxy or ethoxy) (such as, e.g., 2-methoxyethyl (meth)acrylate and 2-ethoxyethyl (meth)acrylate), acrylonitrile, vinyl acetate, vinyl propionate, vinylpyrrolidones (e.g., N-vinyl-2-pyrrolidone), vinylcaprolactam, (meth)acrylic acid, 2-hydroxyethyl (meth)acrylate, styrenesulfonic acid, (meth)acrylamide, and 2-aminoethyl (meth)acrylate.

[0020] Those alkyl (meth)acrylates may be used alone or in combination of two or more thereof, and those functional monomers may be used alone or in combination of two or more thereof.

[0021] Examples of the acrylic copolymer pressure-sensitive adhesives include copolymers of 2-ethylhexyl acrylate and acrylic acid, copolymers of 2-ethylhexyl acrylate, N-vinyl-2-pyrrolidone, and acrylic acid, and copolymers of 2-ethylhexyl acrylate and 2-hydroxyethyl acrylate.

[0022] A liquid plasticizing ingredient may be incorporated into the pressure-sensitive adhesive layer (A).

[0023] The liquid plasticizing ingredient is not particularly limited as long as it is liquid at ordinary temperature and compatible with the pressure-sensitive adhesive to be used (e.g., an acrylic copolymer pressure-sensitive adhesive).

[0024] When a liquid plasticizing ingredient compatible with the pressure-sensitive adhesive (acrylic copolymer pressure-sensitive adhesive) is incorporated into the pressure-sensitive adhesive layer and blends with the pressure-sensitive adhesive (acrylic copolymer pressure-sensitive adhesive) to form a stable homogeneous mixture, then it functions to plasticize the pressure-sensitive adhesive layer. The liquid plasticizing ingredient can be incorporated also for the

purpose of further enhancing drug solubility in the pressure-sensitive adhesive.

[0025] The amount of the liquid plasticizing ingredient to be incorporated is generally from 10 to 200 parts by weight, preferably from 25 to 150 parts by weight, per 100 parts by weight of the pressure-sensitive adhesive. When the amount of the liquid plasticizing ingredient incorporated is 10 parts by weight or larger, preferably 25 parts by weight or larger, per 100 parts by weight of the pressure-sensitive adhesive, sufficient effects are assured with respect to plasticization, drug solubility, etc. When the amount of the liquid plasticizing ingredient incorporated is 200 parts by weight or smaller, preferably 150 parts by weight or smaller, per 100 parts by weight of the pressure-sensitive adhesive, the pressure-sensitive adhesive layer can be prevented from having an excessively reduced cohesive force and, hence, from arousing troubles such as adhesive remaining on the skin surface after stripping.

[0026] Examples of the liquid plasticizing ingredient include esters of fatty acids having 12 to 16 carbon atoms, monoglycerides of fatty acids having 8 to 10 carbon atoms, esters of dibasic acids having 6 to 10 carbon atoms, and nonionic surfactants. Such liquid plasticizing ingredients can be used alone or in combination of two or more thereof.

[0027] Although the pressure-sensitive adhesive in the pressure-sensitive adhesive layer (A) may be an uncrosslinked pressure-sensitive adhesive, it is desirable to crosslink the adhesive by an appropriate crosslinking technique especially when a liquid plasticizing ingredient is incorporated. Crosslinking can impart a moderate cohesive force to the pressure-sensitive adhesive layer.

[0028] Crosslinking reactions generally include physical crosslinking by ultraviolet irradiation, electron beam irradiation, and the like and chemical crosslinking with crosslinking agents such as polyisocyanate compounds, organic peroxides, organometallic compounds, metal alcoholates, metal chelate compounds, and polyfunctional compounds. In the invention, however, the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A), which contains a basic drug, and the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B), which will be described later, differ in the method of crosslinking.

[0029] For the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A), which contains a basic drug, crosslinking agents reactive with the basic drug, such as, e.g., polyisocyanate compounds, cannot be used because the basic drug inhibits these crosslinking agents from forming crosslinks. It is therefore necessary that the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A) be crosslinked by a crosslinking treatment in which crosslink formation is not inhibited by the presence of the basic drug.

[0030] Consequently, for crosslinking the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A), use may, for example, be made of: crosslinking treatments with a crosslinking agent which is not inhibited from forming crosslinks by the basic drug, such as, e.g., an organometallic compound (examples of which include zinc acetate, and zinc ammonium glycinate), a metal alcoholate (examples of which include tetraethyl titanate, tetraisopropyl titanate, aluminum isopropylate, and aluminum butylate), or a metal chelate compound (examples of which include diisopropoxy bis(acetylacetone)titanate, tetraoctylene glycol titanate, aluminum isopropylate, (ethyl acetoacetate) aluminum diisopropylate, aluminum tris (ethyl acetoacetate) , and aluminum tris (acetylacetonate)) ; physical crosslinking treatments with ultraviolet irradiation or electron beam irradiation; or the like. Such crosslinking techniques may be used alone or in combination of two or more thereof.

[0031] The drug to be contained in the pressure-sensitive adhesive layer (A) is not particularly limited as long as it is a basic drug capable of being percutaneously absorbed. Examples thereof include heterocyclic derivatives which are not in the form of a pharmacologically acceptable salt but in a free form and have within the drug molecule at least one member selected from carboxylic acid derivatives, amino acid derivatives, amine derivatives, amic acid derivatives, aromatic amine derivatives, and a nitrogen atom.

[0032] Specific examples of the drug to be contained in the pressure-sensitive adhesive layer (A) include metoprolol, propranolol, azelastine, diazepam, clonidine, bisoprolol, pindolol, ifenprodil, and metoclopramide.

[0033] The basic drug can be incorporated into the pressure-sensitive adhesive layer (A) in the form of a solution or dispersion.

[0034] The basic drug to be contained in the pressure-sensitive adhesive layer (A) may be either a systemic drug or a topical drug.

[0035] Examples of the systemic drug include corticosteroids, analgetic anti-inflammatory agents, hypnotic sedatives, tranquilizing agents, antihypertensives, hypotensive diuretics, antibiotics, anesthetics, antibacterials, antifungal agents, vitamins, coronary vasodilators, antihistaminics, antitussives, sexual hormones, antidepressants, cerebral vasodilators, antiemetics, antitumor agents, and biodrugs. Examples of the topical drug include topical anesthetics, dental antibiotics, bactericidal disinfectants, infection preventive/therapeutic agents, anti-inflammatory agents, and adrenal cortex hormones.

[0036] The content of the basic drug in the pressure-sensitive adhesive layer (A) is in the range of generally from 0.2 to 80% by weight, preferably from 1 to 60% by weight, based on the whole weight of the pressure-sensitive adhesive layer (A).

[0037] The pressure-sensitive adhesive to be used in the pressure-sensitive adhesive layer (B) is not particularly limited as long as it has pressure-sensitive adhesive properties at ordinary temperature. However, acrylic copolymer

pressure-sensitive adhesives are preferred from the standpoints of adhesion to the skin, drug solubility, drug stability, and reactivity in crosslinking. A single pressure-sensitive adhesive or a combination of two or more pressure-sensitive adhesives may be used. The acrylic copolymer pressure-sensitive adhesives for use in the pressure-sensitive adhesive layer (B) are not particularly limited, and examples thereof include copolymers of at least one alkyl (meth)acrylate with at least one functional monomer. The copolymers of at least one alkyl (meth)acrylate with at least one functional monomer preferably are copolymers obtained by copolymerizing from 60 to 98% by weight, preferably from 65 to 97% by weight, of at least one alkyl (meth)acrylate with from 2 to 40% by weight, preferably from 3 to 35% by weight, of at least one functional monomer (provided that the sum of the monomers is 100% by weight).

[0038] Examples of the alkyl (meth)acrylate include the esters obtained from acrylic or methacrylic acid and linear or branched, primary, secondary, or tertiary alcohols in which the alkyl group has 4 to 12 carbon atoms.

[0039] Specific examples of the alkyl (meth)acrylate include the same alkyl (meth)acrylates as those enumerated hereinabove with regard to the pressure-sensitive adhesive layer (A).

[0040] Examples of the functional monomer include functional monomers having at least one unsaturated double bond in the molecule and further having one or more functional groups selected, for example, from the group consisting of carboxyl, hydroxyl, sulfo, amino, amido, alkoxyl, cyano, and acyloxy groups as or in a side chain. Specific examples of the functional monomer include alkoxyl-modified alkyl (meth)acrylate monomers obtained by modifying the alkyl group of an alkyl (meth)acrylate with a linear or branched alkoxyl group having 1 to 4 carbon atoms (e.g., methoxy or ethoxy) (such as, e.g., 2-methoxyethyl (meth)acrylate and 2-ethoxyethyl (meth)acrylate), acrylonitrile, vinyl acetate, vinyl propionate, vinylpyrrolidones (e.g., N-vinyl-2-pyrrolidone), vinylcaprolactam, (meth)acrylic acid, 2-hydroxyethyl (meth)acrylate, styrenesulfonic acid, (meth)acrylamide, and 2-aminoethyl (meth)acrylate.

[0041] Those alkyl (meth)acrylates may be used alone or in combination of two or more thereof, and those functional monomers may be used alone or in combination of two or more thereof.

[0042] Examples of the acrylic copolymer pressure-sensitive adhesives include the same acrylic pressure-sensitive adhesives as those enumerated hereinabove with regard to the pressure-sensitive adhesive layer (A).

[0043] For crosslinking the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B), a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate compound may be used. In other words, the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) is substantially devoid of an organometallic compound, metal alcoholate, and metal chelate compound. Examples of the crosslinking agent other than an organometallic compound, metal alcoholate, and metal chelate compound include polyisocyanate compounds, organic peroxides, melamine derivatives, polyfunctional compounds, amino resins, silane compounds, diol compounds, polyol compounds, bisphenol compounds, and sulfides. These crosslinking agents may be used alone or in combination of two or more thereof.

[0044] The pressure-sensitive adhesive layer (B) contains no basic drug just after the production thereof. However, by superposing the pressure-sensitive adhesive layer (A), which contains a basic drug, on the pressure-sensitive adhesive layer (B) thereafter, a concentration gradient is formed and the drug moves into the superposed layers due to the concentration gradient. Usually, the pharmaceutical preparation comes to have a uniform drug concentration. As a result, due to the influence of the basic drug which has moved into the pressure-sensitive adhesive layer (B), the lactic acid contained in the sweat resulting from perspiration during wear is taken up by the pressure-sensitive adhesive layer. In case where the pressure-sensitive adhesive in the pressure-sensitive adhesive layer (B) has been crosslinked with an organometallic compound, metal alcoholate, or metal chelate compound as a crosslinking agent, the lactic acid taken up by the pressure-sensitive adhesive layer acts on crosslinks of the pressure-sensitive adhesive to reduce the cohesive force of the pressure-sensitive adhesive layer and thereby cause a cohesive failure when the pharmaceutical preparation is stripped off. Because of this, the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B), which is located on the side to be applied to the skin, is crosslinked with a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate compound. Thus, a stable pharmaceutical preparation can be obtained in which the pressure-sensitive adhesive layer does not cause a decrease in cohesive force even when the lactic acid contained in sweat is taken up thereby, and which is hence free from a cohesive failure and resultant adhesive remaining when stripped off.

[0045] The amount of the crosslinking agent to be added varies depending on the kinds of the crosslinking agent and pressure-sensitive adhesive. However, the amount thereof is generally in the range of from 0.01 to 2 parts by weight, preferably from 0.03 to 1.5 parts by weight, per 100 parts by weight of the pressure-sensitive adhesive to be crosslinked.

[0046] A liquid plasticizing ingredient may be contained in the pressure-sensitive adhesive layer (B). The liquid plasticizing ingredient is not particularly limited as long as it is liquid at ordinary temperature and compatible with the pressure-sensitive adhesive to be used (e.g., an acrylic copolymer pressure-sensitive adhesive).

[0047] The amount of the liquid plasticizing ingredient to be incorporated in the pressure-sensitive adhesive layer (B) is generally from 10 to 200 parts by weight, preferably from 25 to 150 parts by weight, per 100 parts by weight of the pressure-sensitive adhesive. When the amount of the liquid plasticizing ingredient incorporated is 10 parts by

weight or larger, preferably 25 parts by weight or larger, per 100 parts by weight of the pressure-sensitive adhesive, sufficient effects are obtained with respect to plasticization, drug solubility, etc. When the amount of the liquid plasticizing ingredient incorporated is 200 parts by weight or smaller, preferably 150 parts by weight or smaller, per 100 parts by weight of the pressure-sensitive adhesive, the pressure-sensitive adhesive layer can be prevented from having an excessively reduced cohesive force and, hence, from arousing troubles such as adhesive remaining on the skin surface after stripping.

[0048] From the standpoints of preventing delamination at the interface between the pressure-sensitive adhesive layers (A) and (B) after the bonding of the two pressure-sensitive adhesive layers, accelerating the movement of the drug from one to the other pressure-sensitive adhesive layer, and improving adhesion between the two pressure-sensitive adhesive layers, it is preferred that the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) should have the same composition. The term "same composition" implies that the pressure-sensitive adhesives are of the same kind or that when two or more kinds of pressure-sensitive adhesives are used, the two layers are equal in the kinds of pressure-sensitive adhesives and in the proportions thereof.

[0049] The thicknesses of the pressure-sensitive adhesive layer (A) and pressure-sensitive adhesive layer (B) are such that the total thickness of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive layer (B) superposed thereon is generally from 20 to 200 μm, preferably from 40 to 150 μm, from the standpoints of applicability to the skin and strippability. Although the pressure-sensitive adhesive layer (A) and pressure-sensitive adhesive layer (B) each may have any desired thickness, the ratio of the thickness of the pressure-sensitive adhesive layer (A) to that of the pressure-sensitive adhesive layer (B) is generally from 1:1 to 20:1, preferably from 2:1 to 15:1.

[0050] Additives may be incorporated into each of the pressure-sensitive adhesive layer (A) and pressure-sensitive adhesive layer (B) according to need. Examples thereof include antioxidants, various pigments, various fillers, stabilizers, drug dissolution aids, and drug dissolution inhibitors.

[0051] The percutaneous absorption-type pharmaceutical preparation of the invention can be produced, for example, by a process comprising the following steps (1) and (2).

[0052] Namely, the pharmaceutical preparation can be produced through:

step (1) of forming a pressure-sensitive adhesive layer (A) comprising a pressure-sensitive adhesive and a basic drug on one side of a substrate; and

step (2) of crosslinking a pressure-sensitive adhesive with a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate compound in the absence of any basic drug to obtain a crosslinked pressure-sensitive adhesive and forming a pressure-sensitive adhesive layer (B) comprising the crosslinked pressure-sensitive adhesive on the pressure-sensitive adhesive layer (A).

[0053] In step (1), a pressure-sensitive adhesive layer (A) can be formed, for example, by a method which comprises dissolving or dispersing a pressure-sensitive adhesive (e.g., an acrylic copolymer pressure-sensitive adhesive) and a basic drug in a solvent or dispersion medium optionally together with a crosslinking agent, a liquid plasticizing ingredient, and other additives, applying the resultant solution or dispersion to one side of a substrate, and drying the coating to form the pressure-sensitive adhesive layer (A). An alternative method is that comprising applying the solution or dispersion to a separator (e.g., a polyester film treated with a releasant), drying the coating to form a pressure-sensitive adhesive layer, and then transferring the pressure-sensitive adhesive layer to one side of a substrate to form the pressure-sensitive adhesive layer (A) .

[0054] In step (2), a pressure-sensitive adhesive layer (B) can be formed, for example, in the following manner. A pressure-sensitive adhesive (e.g., an acrylic copolymer pressure-sensitive adhesive) and a crosslinking agent which is other than an organometallic compound, metal alcoholate, and metal chelate are dissolved or dispersed in a solvent or dispersion medium optionally together with a liquid plasticizing ingredient and other additives. The resultant solution or dispersion is applied to one side of a separator (e.g., a polyester film treated with a releasant) and the coating is dried to form a pressure-sensitive adhesive layer comprising a crosslinked pressure-sensitive adhesive. Thereafter, this pressure-sensitive adhesive layer is bonded to the pressure-sensitive adhesive layer (A) by a known method so that the pressure-sensitive adhesive layers come into direct contact with each other. Thus, the pressure-sensitive adhesive layer (B) can be formed. As the separator, the release sheet which will be described later may be used.

[0055] The solvent or dispersion medium to be used for forming the pressure-sensitive adhesive layer (A) is not particularly limited, and can be selected from solvents or dispersion media ordinary used for pressure-sensitive adhesives while taking into consideration the kind of the pressure-sensitive adhesive, reactivity with the drug, etc. Examples thereof include ethyl acetate, toluene, hexane, 2-propanol, methanol, and ethanol.

[0056] The solvent or dispersion medium to be used for forming the pressure-sensitive adhesive layer (B) is not particularly limited, and can be selected from solvents or dispersion media ordinary used for pressure-sensitive adhesives while taking into consideration the kind of the pressure-sensitive adhesive, reactivity with the crosslinking agent,

etc. Examples thereof include ethyl acetate, toluene, hexane, 2-propanol, methanol, and ethanol.

[0057] The pharmaceutical preparation obtained through steps (1) and (2) is a layered product which, just after the production thereof, comprises a drug-containing pressure-sensitive adhesive layer (pressure-sensitive adhesive layer (A)) and a drug-free pressure-sensitive adhesive layer (pressure-sensitive adhesive layer(B)). However, in order for this layered product to be used as a pharmaceutical preparation, it is desirably made to be a stable pharmaceutical preparation finally having an even concentration. Drug movement from one to the other superposed layer may be accelerated by storing the layered product comprising the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive layer (B), for example, at a certain constant temperature.

[0058] It is preferred in the percutaneous absorption-type pharmaceutical preparation of the invention that the exposed side of the pressure-sensitive adhesive layer (B) be covered and protected with a release sheet until just before application to the skin. The release sheet is stripped off to expose the pressure-sensitive adhesive layer surface just before use, and this pharmaceutical preparation is applied to the skin to administer the drug. The release sheet is not particularly limited as long as it can be easily stripped from the pressure-sensitive adhesive layer just before use. For example, use is made of a film of a polyester, poly(vinyl chloride), poly(vinylidene chloride), poly(ethylene terephthalate), or the like in which the side to be in contact with the pressure-sensitive adhesive layer has been treated with a silicone, or of a laminated film obtained by laminating a polyolefin to wood-free paper or glassine paper. The thickness of the release sheet is generally 1,000 μm or smaller, preferably from 30 to 200 μm.

[0059] The shape of the percutaneous absorption-type pharmaceutical preparation of the invention is not particularly limited. Examples thereof include tape forms and sheet forms.

[0060] The dose of the percutaneous absorption-type pharmaceutical preparation of the invention varies depending on the kind of the drug used, the age, body weight, and condition of the patient, etc. Usually, however, the dose for an adult is such that the pharmaceutical preparation containing from 1 to 500 mg of a percutaneously absorbable drug is applied to an area of from 1 to 100 cm^2 and about from once per day to once per 7 days.

[0061] The invention will be explained below in more detail by reference to Examples, Comparative Examples, and Experimental Examples, but the invention should not be construed as being limited by these in any way. In the following description, all parts and percents are by weight.

Preparation of Acrylic Copolymer Pressure-Sensitive Adhesives:

[0062] In an inert gas atmosphere, 95 parts of 2-ethylhexyl acrylate was copolymerized with 5 parts of acrylic acid in ethyl acetate to prepare an acrylic copolymer pressure-sensitive adhesive (hereinafter referred to as "acrylic copolymer pressure-sensitive adhesive (a)").

[0063] In an inert gas atmosphere, 72 parts of 2-ethylhexyl acrylate was copolymerized with 25 parts of N-vinyl-2-pyrrolidone and 3 parts of acrylic acid in ethyl acetate to prepare an acrylic copolymer pressure-sensitive adhesive (hereinafter referred to as "acrylic copolymer pressure-sensitive adhesive (b)").

[0064] In an inert gas atmosphere, 60 parts of 2-ethylhexyl acrylate was copolymerized with 10 parts of 2-hydroxyethyl acrylate and 30 parts of vinyl acetate in ethyl acetate to prepare an acrylic copolymer pressure-sensitive adhesive (hereinafter referred to as "acrylic copolymer pressure-sensitive adhesive (c)").

EXAMPLE 1

[0065] An ethyl acetate solution (pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (A)) containing 46 parts of acrylic copolymer pressure-sensitive adhesive (a), 4 parts of metoprolol, 50 parts of isopropyl myristate (IPM), and 0.3 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a pressure-sensitive adhesive layer (A).

[0066] An ethyl acetate solution (pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (B)) containing 47.9 parts of acrylic copolymer pressure-sensitive adhesive (a), 52.1 part of IPM, and 0.2 parts of a polyisocyanate (Coronate HL (C/HL), manufactured by Nippon Polyurethane Co., Ltd.) was applied to a release sheet made of a polyester (75 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a pressure-sensitive adhesive layer (B).

[0067] Subsequently, the pressure-sensitive adhesive layer (A) was bonded to the pressure-sensitive adhesive layer (B) so that these adhesive layers came into direct contact with each other. Thus, a percutaneous absorption-type pharmaceutical preparation was produced. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours for the purposes of accelerating crosslinking and accelerating drug movement from one to the other layer.

EXAMPLE 2

[0068] A percutaneous absorption-type pharmaceutical preparation was produced in the same manner as in Example 1, except that (ethyl acetoacetate)aluminum diisopropylate was not incorporated into the pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (A). After the production, this pharmaceutical preparation was heated at 70°C for 48 hours as in Example 1.

EXAMPLE 3

[0069] A percutaneous absorption-type pharmaceutical preparation was produced in the same manner as in Example 1, except that the pressure-sensitive adhesive solutions were applied in such respective amounts as to give a pressure-sensitive adhesive layer (A) having a thickness of 60 μm on a dry basis and a pressure-sensitive adhesive layer (B) having a thickness of 20 μm on a dry basis. After the production, the pharmaceutical preparation was heated at 70°C for 48 hours as in Example 1.

EXAMPLE 4

[0070] An ethyl acetate solution (pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (A)) containing 45 parts of acrylic copolymer pressure-sensitive adhesive (b), 10 parts of propranolol, 45 parts of IPM, and 0.3 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a pressure-sensitive adhesive layer (A).

[0071] An ethyl acetate solution (pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (B)) containing 50 parts of acrylic copolymer pressure-sensitive adhesive (b), 50 parts of IPM, and 0.3 parts of a polyisocyanate (C/HL, manufactured by Nippon Polyurethane Co., Ltd.) was applied to a release sheet made of a polyester (75 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a pressure-sensitive adhesive layer (B).

[0072] Subsequently, the pressure-sensitive adhesive layer (A) was bonded to the pressure-sensitive adhesive layer (B) so that these adhesive layers came into direct contact with each other. Thus, a percutaneous absorption-type pharmaceutical preparation was produced. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours for the purposes of accelerating crosslinking and accelerating drug movement from one to the other layer.

EXAMPLE 5

[0073] A percutaneous absorption-type pharmaceutical preparation was produced in the same manner as in Example 4, except that (ethyl acetoacetate)aluminum diisopropylate was not incorporated into the pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (A). After the production, this pharmaceutical preparation was heated at 70°C for 48 hours as in Example 4.

EXAMPLE 6

[0074] An ethyl acetate solution (pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (A)) containing 50 parts of acrylic copolymer pressure-sensitive adhesive (c), 10 parts of azelastine, 40 parts of IPM, and 0.3 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 60 μm on a dry basis. The coating was dried to form a pressure-sensitive adhesive layer (A).

[0075] An ethyl acetate solution (pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (B)) containing 55.6 parts of acrylic copolymer pressure-sensitive adhesive (c), 44.4 parts of IPM, and 0.3 parts of a polyisocyanate (C/HL, manufactured by Nippon Polyurethane Co., Ltd.) was applied to a release sheet made of a polyester (75 μm thick) in such an amount as to result in a thickness of 20 μm on a dry basis. The coating was dried to form a pressure-sensitive adhesive layer (B).

[0076] Subsequently, the pressure-sensitive adhesive layer (A) was bonded to the pressure-sensitive adhesive layer (B) so that these adhesive layers came into direct contact with each other. Thus, a percutaneous absorption-type pharmaceutical preparation was produced. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours for the purposes of accelerating crosslinking and accelerating drug movement from one to the other layer.

EXAMPLE 7

[0077] A percutaneous absorption-type pharmaceutical preparation was produced in the same manner as in Example 6, except that (ethyl acetoacetate)aluminum diisopropylate was not incorporated into the pressure-sensitive adhesive solution for pressure-sensitive adhesive layer (A). After the production, this pharmaceutical preparation was heated at 70°C for 48 hours as in Example 6.

COMPARATIVE EXAMPLE 1

[0078] An ethyl acetate solution containing 46 parts of acrylic copolymer pressure-sensitive adhesive (a), 4 parts of metoprolol, 50 parts of IPM, and 0.3 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 80 μm on a dry basis. The coating was dried to produce a percutaneous absorption-type pharmaceutical preparation. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours.

COMPARATIVE EXAMPLE 2

[0079] An ethyl acetate solution containing 46 parts of acrylic copolymer pressure-sensitive adhesive (a), 4 parts of metoprolol, and 50 parts of IPM was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a drug-containing pressure-sensitive adhesive layer.

[0080] An ethyl acetate solution containing 47.9 parts of acrylic copolymer pressure-sensitive adhesive (a), 52.1 part of IPM, and 0.3 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to a release sheet made of a polyester (75 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a drug-free pressure-sensitive adhesive layer.

[0081] Subsequently, the drug-containing pressure-sensitive adhesive layer was bonded to the drug-free pressure-sensitive adhesive layer so that these adhesive layers came into direct contact with each other. Thus, a percutaneous absorption-type pharmaceutical preparation was produced. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours.

COMPARATIVE EXAMPLE 3

[0082] An ethyl acetate solution containing 45 parts of acrylic copolymer pressure-sensitive adhesive (b), 10 parts of propranolol, and 45 parts of IPM was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a drug-containing pressure-sensitive adhesive layer.

[0083] An ethyl acetate solution containing 50 parts of acrylic copolymer pressure-sensitive adhesive (b), 50 parts of IPM, and 0.3 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to a release sheet made of a polyester (75 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a drug-free pressure-sensitive adhesive layer.

[0084] Subsequently, the drug-containing pressure-sensitive adhesive layer was bonded to the drug-free pressure-sensitive adhesive layer so that these adhesive layers came into direct contact with each other. Thus, a percutaneous absorption-type pharmaceutical preparation was produced. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours.

COMPARATIVE EXAMPLE 4

[0085] An ethyl acetate solution containing 50 parts of acrylic copolymer pressure-sensitive adhesive (c), 10 parts of azelastine, and 40 parts of IPM was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 60 μm on a dry basis. The coating was dried to form a drug-containing pressure-sensitive adhesive layer.

[0086] An ethyl acetate solution containing 55.6 parts of acrylic copolymer pressure-sensitive adhesive (c), 44.4 parts of IPM, and 0.4 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to a release sheet made of a polyester (75 μm thick) in such an amount as to result in a thickness of 20 μm on a dry basis. The coating was dried to form a drug-free pressure-sensitive adhesive layer.

[0087] Subsequently, the drug-containing pressure-sensitive adhesive layer was bonded to the drug-free pressure-sensitive adhesive layer so that these adhesive layers came into direct contact with each other. Thus, a percutaneous

absorption-type pharmaceutical preparation was produced. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours.

COMPARATIVE EXAMPLE 5

[0088] An ethyl acetate solution containing 45 parts of acrylic copolymer pressure-sensitive adhesive (a), 15 parts of isosorbide dinitrate, 40 parts of IPM, and 0.3 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 60 μm on a dry basis. The coating was dried to produce a percutaneous absorption-type pharmaceutical preparation. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours.

COMPARATIVE EXAMPLE 6

[0089] An ethyl acetate solution containing 47 parts of acrylic copolymer pressure-sensitive adhesive (b), 3 parts of estradiol, 50 parts of IPM, and 0.4 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 60 μm on a dry basis. The coating was dried to produce a percutaneous absorption-type pharmaceutical preparation. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours.

COMPARATIVE EXAMPLE 7

[0090] An ethyl acetate solution containing 47 parts of acrylic copolymer pressure-sensitive adhesive (b), 3 parts of estradiol, and 50 parts of IPM was applied to the nonwoven-fabric side of a laminated film composed of a nonwoven polyester fabric (basis weight, 12 g/m^2) and a polyester film (2 μm thick) in such an amount as to result in a thickness of 40 μm on a dry basis. The coating was dried to form a drug-containing pressure-sensitive adhesive layer.

[0091] An ethyl acetate solution containing 48.5 parts of acrylic copolymer pressure-sensitive adhesive (b), 51.5 parts of IPM, and 0.4 parts of (ethyl acetoacetate)aluminum diisopropylate was applied to a release sheet made of a polyester (75 μm thick) in such an amount as to result in a thickness of 20 μm on a dry basis. The coating was dried to form a basic-drug-free pressure-sensitive adhesive layer.

[0092] Subsequently, the basic-drug-containing pressure-sensitive adhesive layer was bonded to the basic-drug-free pressure-sensitive adhesive layer so that these adhesive layers came into direct contact with each other. Thus, a percutaneous absorption-type pharmaceutical preparation was produced. After the production, this pharmaceutical preparation was heated at 70°C for 48 hours.

[0093] In Tables 1 and 2 are shown the compositions and dry thicknesses of the pressure-sensitive adhesive layers in each of Examples 1 to 7 and Comparative Examples 1 to 7.

Table 1

Example No.	Pressure-Sensitive Adhesive Layer (A)					Pressure-Sensitive Adhesive Layer (B)			
	Pressure-sensitive adhesive (parts)	Percutaneously absorbable drug (parts)	Liquid plasticizing ingredient (parts)	Cross-linking agent (parts)	Dry thickness (μm)	Pressure-sensitive adhesive (parts)	Liquid plasticizing ingredient (parts)	Cross-linking agent (parts)	Dry thickness (μm)
Ex. 1	adhesive (a) 46	metoprolol 4	IPM 50	ALCH 0.3	40	adhesive (a) 47.9	IPM 52.1	C/HL 0.2	40
Ex. 2	adhesive (a) 46	metoprolol 4	IPM 50	-	40	adhesive (a) 47.9	IPM 52.1	C/HL 0.2	40
Ex. 3	adhesive (a) 46	metoprolol 4	IPM 50	ALCH 0.3	60	adhesive (a) 47.9	IPM 52.1	C/HL 0.2	20
Ex. 4	adhesive (b) 45	propranol 10	IPM 45	ALCH 0.3	40	adhesive (b) 50	IPM 50	C/HL 0.3	40
Ex. 5	adhesive (b) 45	propranol 10	IPM 45	-	40	adhesive (b) 50	IPM 50	C/HL 0.3	40
Ex. 6	adhesive (c) 50	azelastine 10	IPM 40	ALCH 0.3	60	adhesive (c) 55.6	IPM 44.4	C/HL 0.3	20
Ex. 7	adhesive (c) 50	azelastine 10	IPM 40	-	60	adhesive (c) 55.6	IPM 44.4	C/HL 0.3	20

IPM: isopropyl myristate

ALCH: (ethyl acetoacetate)aluminum diisopropylate

C/HL: polyisocyanate

Table 2

Comparative Example No.	Drug-Containing Pressure-Sensitive Adhesive Layer (A)					Drug-Free Pressure-Sensitive Adhesive Layer (B)			
	Pressure-sensitive adhesive (parts)	Percutaneously absorbable drug (parts)	Liquid plasticizing ingredient (parts)	Cross-linking agent (parts)	Dry thickness (μm)	Pressure-sensitive adhesive (parts)	Liquid plasticizing ingredient (parts)	Cross-linking agent (parts)	Dry thickness (μm)
Comp. Ex. 1	adhesive (a) 46	metoprolol 4	IPM 50	ALCH 0.3	80	-	-	-	-
Comp. Ex. 2	adhesive (a) 46	metoprolol 4	IPM 50	-	40	adhesive (a) 47.9	IPM 52.1	ALCH 0.3	40
Comp. Ex. 3	adhesive (b) 45	propranol 10	IPM 45	-	40	adhesive (b) 50	IPM 50	ALCH 0.3	40
Comp. Ex. 4	adhesive (c) 50	azelastine 10	IPM 40	-	60	adhesive (c) 55.6	IPM 44.4	ALCH 0.4	20
Comp. Ex. 5	adhesive (a) 45	isosorbide dinitrate 15	IPM 40	ALCH 0.3	60	-	-	-	-
Comp.- Ex. 6	adhesive (b) 47	estradiol 3	IPM 50	ALCH 0.4	60	-	-	-	-
Comp. Ex. 7	adhesive (b) 47	estradiol 3	IPM 50	-	40	adhesive (b) 48.5	IPM 51.5	ALCH 0.4	20

IPM: isopropyl myristate

ALCH: (ethyl acetoacetate)aluminum diisopropylate

C/HL: polyisocyana

EP 1 369 112 A1

EXPERIMENTAL EXAMPLES

[0094] The percutaneous absorption-type pharmaceutical preparations produced in the Examples and Comparative Examples given above were subjected to the lactic acid uptake test and adhesive force measurement shown below.

EXPERIMENTAL EXAMPLE 1 - Lactic Acid Uptake Test

[0095] The amount of lactic acid taken up by a pharmaceutical preparation was measured by the following method. In a petri dish was placed 15 mL of 1% aqueous lactic acid solution. A 30-cm^2 specimen punched out of the pharmaceutical preparation was immersed therein for 10 minutes and the excess lactic acid solution was then removed (lactic acid immersion treatment). This pharmaceutical preparation was chopped and immersed in 15 mL of distilled water placed in a meyer flask, and 5 mL of an internal standard solution was added thereto. This mixture was shaken at 40°C for 1 hour for extraction. The resultant extract was examined by HPLC under the following conditions to determine the amount of lactic acid absorbed in the pharmaceutical preparation. The results obtained are shown in Table 3.

[0096] The HPLC conditions used are as follows.

(Conditions for Lactic Acid Determination)

[0097]

Column	YMC-Pack PolymerC18 (ϕ4.6 x 250 mm)
Moving phase	0.1% phosphoric acid
Column temperature	25°C
Flow rate	1.0 mL/min
Detection method	absorbance measurement at UV 210 nm
Internal standard solution	aqueous acetic acid solution (0.5→1000)

EXPERIMENTAL EXAMPLE 2 - Adhesive Force Measurement

[0098] The adhesive force of each percutaneous absorption-type pharmaceutical preparation produced (hereinafter referred to as "adhesive force 1") and the adhesive force of a sample obtained by subjecting each percutaneous absorption-type pharmaceutical preparation to a lactic acid immersion treatment under the same conditions as in the lactic acid uptake test described above, applying the treated pharmaceutical preparation to a release sheet, and then allowing it to stand for 24 hours (hereinafter referred to as "adhesive force 2") each were measured by the following method. The pharmaceutical preparation was cut into a strip having a width of 24 mm. The pressure-sensitive adhesive side of this strip of the pharmaceutical preparation was applied to a Bakelite plate and press-bonded thereto by rolling a 300-g roller forward and backward once thereon. Thereafter, the pharmaceutical preparation was peeled from the plate in the 180° direction at a rate of 300 mm/min and the adhesive force in this peeling was measured. The results obtained are shown in Table 3.

Table 3

	Amount of lactic acid taken up (mg/cm^2)	Adhesive forces (g/24 mm)	
		Adhesive force 1	Adhesive force 2
Example 1	0.042	98	102
Example 2	0.045	92	95
Example 3	0.038	89	90
Example 4	0.052	125	119
Example 5	0.048	132	129
Example 6	0.032	112	109
Example 7	0.036	115	120
Comparative Example 1	0.044	96	425
Comparative Example 2	0.051	94	512
Comparative Example 3	0.046	122	621

Table 3 (continued)

	Amount of lactic acid taken up (mg/cm^2)	Adhesive forces (g/24 mm)	
		Adhesive force 1	Adhesive force 2
Comparative Example 4	0.035	109	385
Comparative Example 5	0.002	87	88
Comparative Example 6	0.003	116	121
Comparative Example 7	0.004	118	124

[0099] Table 3 shows the following. The basic-drug-containing percutaneous absorption-type pharmaceutical preparations of Examples 1 to 7 according to the invention each took up lactic acid but had almost no difference between adhesive force 1 and adhesive force 2. Namely, these were stable pharmaceutical preparations unsusceptible to the influence of lactic acid.

[0100] In contrast, the basic-drug-containing pharmaceutical preparations of Comparative Examples 1 to 4 each were an unstable preparation which took up lactic acid and suffered a considerable change in adhesive force due to the lactic acid.

[0101] The basic-drug-free pharmaceutical preparations of Comparative Examples 5 to 7 each showed no difference between adhesive force 1 and adhesive force 2. This indicates that in basic-drug-free pharmaceutical preparations, lactic acid is not taken up by the preparations depending on the kind of the drug.

[0102] The percutaneous absorption-type pharmaceutical preparation of the invention can be prevented from suffering a decrease in the cohesive force of the pressure-sensitive adhesive layer when lactic acid as a sweat component is taken up. Consequently, the present invention provides: a stable percutaneous absorption-type pharmaceutical preparation for the percutaneous absorption of basic drugs which does not cause a decrease in the cohesive force of the pressure-sensitive adhesive layer even in the presence of sweat components due to perspiration during wear and which is free from a cohesive failure and resultant adhesive remaining when stripped off; and a process for producing the pharmaceutical preparation.

[0103] While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the scope thereof.

[0104] This application is based on Japanese patent application No. 2002-164973 filed June 5, 2002, the entire contents thereof being hereby incorporated by reference.

Claims

1. A percutaneous absorption-type pharmaceutical preparation which comprises a substrate and, superposed on one side thereof in this order,

   a pressure-sensitive adhesive layer (A) comprising a pressure-sensitive adhesive and a basic drug, and
   a pressure-sensitive adhesive layer (B) comprising a pressure-sensitive adhesive crosslinked with a crosslinking agent other than an organometallic compound, metal alcoholate, and metal chelate compound.

2. The percutaneous absorption-type pharmaceutical preparation of claim 1, wherein the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) is a pressure-sensitive adhesive crosslinked with one or more crosslinking agents selected from the group consisting of polyisocyanate compounds, organic peroxides, melamine derivatives, polyfunctional compounds, amino resins, silane compounds, diol compounds, polyol compounds, bisphenol compounds, and sulfides.

3. The percutaneous absorption-type pharmaceutical preparation of claim 1, wherein at least one of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive layer (B) contain a liquid plasticizing ingredient.

4. The percutaneous absorption-type pharmaceutical preparation of claim 1, wherein the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) have the same composition.

5. The percutaneous absorption-type pharmaceutical preparation of claim 1, wherein at least one of the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (A) and the pressure-sensitive adhesive of the pressure-sensitive adhesive layer (B) each are an acrylic copolymer pressure-sensitive adhesive.

6. The percutaneous absorption-type pharmaceutical preparation of claim 5, wherein the acrylic copolymer pressure-sensitive adhesive of each of the pressure-sensitive adhesive layer (A) or the pressure-sensitive adhesive layer (B) comprises a copolymer obtained by copolymerizing from 60 to 98% by weight of at least one alkyl (meth) acrylate in which the alkyl has 4 to 12 carbon atoms with from 2 to 40% by weight of at least one functional monomer.

7. The percutaneous absorption-type pharmaceutical preparation of claim 6, wherein the functional monomer is a monomer having one or more substituents selected from the group consisting of a carboxyl group, a hydroxyl group, a sulfo group, an amino group, an amido group, an alkoxyl group, a cyano group, and an acyloxy group.

8. The percutaneous absorption-type pharmaceutical preparation of claim 7, wherein the functional monomer is one or more monomers selected from the group consisting of (meth)acrylic acid, 2-hydroxyethyl (meth)acrylate, styrenesulfonic acid, (meth)acrylamide, vinylpyrrolidone, 2-aminoethyl (meth)acrylate, acrylonitrile, 2-methoxyethyl (meth)acrylate, and vinyl acetate.

9. A process for producing a pharmaceutical preparation of the percutaneous absorption-type which comprises:

(1) a step of forming a pressure-sensitive adhesive layer (A) comprising a pressure-sensitive adhesive and a basic drug on one side of a substrate; and
(2) a step of crosslinking a pressure-sensitive adhesive with a crosslinking agent other than an organometallic compound, metal alcoholate, and metal chelate compound in the absence of any basic drug to obtain a crosslinked pressure-sensitive adhesive and forming a pressure-sensitive adhesive layer (B) comprising the crosslinked pressure-sensitive adhesive on the pressure-sensitive adhesive layer (A).

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 03 01 2812

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 4 585 452 A (SABLOTSKY STEVEN) 29 April 1986 (1986-04-29) * column 6, line 67 - column 7, line 2; claim 1; examples I-IV *	1-9	A61K9/70 A61K47/32
A	US 5 186 938 A (SABLOTSKY STEVEN ET AL) 16 February 1993 (1993-02-16) * claims 1-8 *	1-9	
A	EP 0 531 938 A (NITTO DENKO CORP) 17 March 1993 (1993-03-17) * claim 2 *	1-9	
A	EP 1 188 436 A (NITTO DENKO CORP) 20 March 2002 (2002-03-20) * page 7, line 11 - page 7, line 58; examples 1,2 *	1-9	
A	US 5 393 529 A (HOFFMANN HANS-RAINER ET AL) 28 February 1995 (1995-02-28) * claims 1-8; examples 1,3 *	1-9	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	18 September 2003	ESTANOL, I

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 03 01 2812

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-09-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4585452 A	29-04-1986	NONE	
US 5186938 A	16-02-1993	AT 59302 T	15-01-1991
		AU 576889 B2	08-09-1988
		AU 4676185 A	25-02-1986
		DE 3581188 D1	07-02-1991
		EP 0190262 A1	13-08-1986
		FI 861177 A ,B,	20-03-1986
		HK 94093 A	17-09-1993
		JP 4040326 B	02-07-1992
		JP 61502760 T	27-11-1986
		NO 861101 A	20-03-1986
		NO 171950 B	15-02-1993
		WO 8600814 A1	13-02-1986
		ES 8800058 A1	01-01-1988
EP 0531938 A	17-03-1993	JP 5065223 A	19-03-1993
		JP 5065224 A	19-03-1993
		JP 3014188 B2	28-02-2000
		JP 6023029 A	01-02-1994
		JP 2971998 B2	08-11-1999
		JP 5065460 A	19-03-1993
		JP 5139960 A	08-06-1993
		CA 2077369 A1	10-03-1993
		DE 69216963 D1	06-03-1997
		DE 69216963 T2	15-05-1997
		EP 0531938 A1	17-03-1993
		ES 2097845 T3	16-04-1997
EP 1188436 A	20-03-2002	JP 2002080349 A	19-03-2002
		CA 2356743 A1	05-03-2002
		CN 1349794 A	22-05-2002
		EP 1188436 A2	20-03-2002
		US 2002106401 A1	08-08-2002
US 5393529 A	28-02-1995	DE 3933460 A1	18-04-1991
		AT 126069 T	15-08-1995
		AU 637637 B2	03-06-1993
		AU 6312890 A	11-04-1991
		CA 2027053 A1	07-04-1991
		CS 9004859 A2	15-10-1991
		DE 59009495 D1	14-09-1995
		DK 421454 T3	09-08-1995
		EP 0421454 A2	10-04-1991
		ES 2078929 T3	01-01-1996
		FI 100380 B1	28-11-1997

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 03 01 2812

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-09-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5393529 A		GR 3017851 T3	31-01-1996
		GR 3033662 T3	31-10-2000
		HR 930676 A1	31-10-1994
		HU 56290 A2	28-08-1991
		IE 903572 A1	10-04-1991
		IL 95776 A	07-10-1994
		JP 2766864 B2	18-06-1998
		JP 3204811 A	06-09-1991
		KR 9604300 B1	30-03-1996
		NO 904338 A	08-04-1991
		NZ 235581 A	26-03-1993
		PL 287200 A1	12-08-1991
		PT 95505 A ,B	14-08-1991
		SI 9011847 A ,B	30-06-1998
		SK 279514 B6	02-12-1998
		ZA 9007969 A	28-08-1991

EPO FORM P0459